Excerpted from PAR-11-157 "NIDDK Multi-Center Clinical Study Cooperative Agreements (U01)"

The guidelines available here use language posted in the original funding opportunity announcement (FOA) and do not replace or modify the criteria established in the full announcement. If you have any questions, contact the Scientific Review Officer (SRO) in charge of the review panel. SRO contact information for your application can be found in eRA Commons.

Overview

NIDDK will support investigator-initiated, multi-center clinical studies through a two part grant process: Part (1) is an implementation planning (U34) grant followed by Part (2) a multi-center clinical study cooperative agreement (U01). **The U01 application you are evaluating emerged from the U34 project and was submitted for the second part of the process in response to PAR11-157, "NIDDK MULTI-CENTER CLINICAL STUDY COOPERATIVE AGREEMENTS (U01)".**

BACKGROUND

Part 1. Implementation Planning (U34) Grant. NIDDK will support clinical study planning (U34) grants for multi-center clinical studies. These grants are intended to support all administrative study group activities that are required in order to begin recruitment of subjects. These activities include, but are not limited to: establishing the research team, developing tools for data management and oversight of the research, defining recruitment strategies, finalizing the protocol and investigators brochure, writing of the Manual of Operations, establishing a data and safety monitoring plan, and initiating the IRB approval process. The U34 grant will provide up to two years of support. U34 applications are peer reviewed by special emphasis panels convened by the NIDDK Review Branch. The product of an awarded and successful U34 will be an application to conduct the clinical study. It is expected that receipt of a U34 grant will lead to the timely submission of an application (U01) for support of the full-scale study, incorporating the elements developed under the planning grant. Prospective applicants should note that funding of a U34 does not guarantee or imply funding for a subsequent U01 application.

Part 2. Multi-Center Clinical Study Cooperative Agreement (U01). NIDDK will accept, peer review, and consider for funding applications for investigator-initiated, multi-center clinical studies from U34 awardees only, except when an exemption from this requirement has been obtained from NIDDK. An applicant who can demonstrate that all the work required for a submission of a multi-center clinical study application has been completed may request an exemption from the prerequisite of holding a U34 award prior to submitting the U01 application.

The materials developed in the U34 phase will allow the applicant to initiate study staff training followed by study subject recruitment soon after an expedited peer review and final NIDDK approval of the clinical study application. In order not to delay the initiation of the study, the peer review and award of the grant will be completed within four months of the receipt of the application when possible. *The purpose of the review of the U01 is to insure that the applicant has accomplished the milestones established in the U34 and to make sure that the scientific landscape has not changed and that the proposed study is still of scientific importance and is feasible.*

The U01 application should highlight any changes to the protocol and all key decisions made during the U34 period, and should include all DSMB recommendations. The application should include a clear discussion of the power calculations and the feasibility of recruitment.

Further information regarding the U34/U01 process, including frequently asked questions (FAQs), can be found on the U34 and U01 About Funding Mechanism pages.

Detailed Reviewer Guidelines

Written Critiques

- The format of the critiques should follow the structured U01 Critique Template provided on the CD, or downloaded from the Internet Assisted Review (IAR) site in "Meeting Materials".
- Each core criterion and additional review criteria are represented in the reviewer template and should be commented on, listing the strengths and weaknesses of each.

- In some cases it is perfectly acceptable to use short bulleted sentences as long as your points are clear. However it is also acceptable for you to write a full paragraph or 2 if you feel that is the best way to communicate your impressions. Do not sacrifice clarity in the pursuit of brevity. The goal is to provide the maximum and most pertinent information in a concise manner.
- After considering all of the review criteria, briefly summarize the strengths and weaknesses of the application in the Overall Impact section of the template.
- The criterion scores may be changed during FINAL SCORING on your electronic or paper Voter/Scoring Sheet, or following the review meeting during the EDIT phase. The Final Overall Score however is the one assigned just prior to the conclusion of the meeting. Please do not write your criterion scores on the critique template

Preliminary Scores

- Each of the five (5) core review criterion (Significance, Investigators, Innovation, Approach, and Environment) should be given a score using the nine-point rating scale (1 to 9, Exceptional to Poor).
- Reviewers will also provide an overall impact/priority score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the review criteria and additional review criteria (as applicable for the project proposed). It is not an average of the 5 criteria scores.
- The criterion scores and the Overall score for the applications should be entered in the meeting Internet Assisted Review (IAR) site in NIH Commons before the review meeting using the same page that is used for submitting the preliminary impact/priority score and critique.

Review Criteria

Only the review criteria described below will be considered in the review process. *For this particular announcement, note the following: The NIDDK will certify that the applicant has achieved the milestones of the Part 1 U34 grant. The applicant will not be allowed to proceed with the multi-center clinical study cooperative agreement (U01) unless all materials required for training of study staff and recruitment of study subjects have been developed.* ***Therefore, the review process will focus on evaluating whether the proposed study is still of scientific importance and is feasible.***

Overall Impact

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

1. Significance: Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

2. Investigators: Are the PD/PIs, collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project? Does the application include a clear statement of the leadership and organization of the study, including evidence that the principal investigator has experience in the administration of a complex

study?

3. Innovation: Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

4. Approach: Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

- If the project involves clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?
- Is the experimental design adequate and does it address the following:
    - Translation of the clinical question into a statistical hypothesis;
    - endpoint(s) and data to be collected, including relevance to the clinical and statistical hypothesis being tested;
    - sample size and duration of the study;
    - randomization, masking (if appropriate), and inclusion/exclusion criteria;
    - plans to standardize and monitor adherence to the clinical protocol, and methods for standardization of procedures for data management and quality control;
    - availability of the requisite eligible patient pool; availability of children, women and minority individuals as study participants and specific recruitment and retention plans for their inclusion;
    - the status of evidence showing whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected;
    - plans for training of study staff;
    - plans for recruitment outreach and, as appropriate, follow-up procedures to ensure collection of data at stated intervals; and data analysis plan?

5. Environment: Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements? Is the study population required for the proposed study available?

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact/priority score, but will not give separate scores for these items.

Protection for Human Subjects: For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Inclusion of Women, Minorities and Children: When the proposed project involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Vertebrate Animals: The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Biohazards: Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed

Resubmission Applications: For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

Renewals

For Renewals, the committee will consider the progress made in the last funding period.

Revisions

Not Applicable

Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact/priority score.

Applications from Foreign Organizations: Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research: Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genome Wide Association Studies (GWAS).

Budget and Period of Support: Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research. The priority score should **not** be affected by the evaluation of the budget.